

EXHIBIT B

SCHERING-PLOUGH CORPORATION

RECORD OF INVENTION

DISCLOSURE NO. 3669**IMPORTANT:**

1. Fill out this form completely. If no experiments or tests have been performed, please indicate.
2. Supplement this record with a complete description of the invention including drawings, if possible, discussion of utility, variations, important features and advantages. Where the invention is a chemical compound, the process (or processes) for preparing the inventive compounds disclosed must be shown. This process must start from known compounds. Please indicate references for recently published compounds.
3. Please remember that every page of this record must be signed by the suggested inventor or all the suggested inventors and witnessed, the signature of each suggested inventor and witness must be dated, and the original sent immediately to the Patent Department. The suggested inventor(s) must cross out the remaining blank portion of each page and sign each page where indicated.

SUBJECT MATTER: The use of azetidinone compounds (ezetimibe, SCH58235) to inhibit the intestinal absorption of plant sterols.SUGGESTED INVENTOR(S): Harry R. Davis, Jr.FIRST DISCLOSED TO Glen Tetzloff DATE _____

FIRST DRAWING OR WRITTEN DESCRIPTION _____ DATE _____

FIRST EXPERIMENTS AND/OR TESTS _____ DATE _____

One of the following boxes (A - F) MUST be checked.

This invention was:

- ☒ A. not derived from DNA sequence information
☐ B. derived from DNA sequence information obtained from public or SP databases
☐ C. derived from DNA sequence information obtained from Inocyte databases
☐ D. derived from DNA sequence information obtained from the HGS database
☐ E. derived from DNA sequence information obtained from the GTC/ PathoGenome™ database
☐ F. derived from DNA sequence information obtained from other source: please specify _____

If Box B, C, D, E or F is checked, indicate Notebook Number and Page Reference to document data base source:

Notebook Number: 39040 Page Number(s): 64-75 Date: _____**Notebook Documentation ascertained by:**

Arthur Brown

Name

Signature Arthur Brown

Date _____

Notebook Documentation reviewed and approved by (Senior Director or above):

John C. Hunter

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WITNESSED AND UNDERSTOOD BY:

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Acknowledged by: Patent Dept.Signature Patent Dept.

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SUGGESTED INVENTORS

Harry R. Davis, Jr.

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BRIEF DESCRIPTION INCLUDING UTILITY OF THE INVENTION (WITH SKETCH IF APPROPRIATE). TRY TO GIVE BOTH BROAD SCOPE AND PREFERRED EMBODIMENTS. INCLUDE "SCH" NUMBERS IF AVAILABLE.

The use of azelidinone compounds (ezetimibe, SCH58235) to inhibit the absorption of plant sterols.

Azelidinone compounds, like ezetimibe (SCH58235) have been found to be potent cholesterol absorption inhibitors, which reduce plasma cholesterol levels and inhibit atherosclerosis. Cholesterol absorption studies with SCH58235 in mice using a fecal isotope ratio method revealed an unexpected finding that SCH58235 inhibited the absorption of the plant sterol sitosterol. Triflated sitosterol was used as an "unabsorbable" marker to compare to the absorption of [14C]-cholesterol in a mouse fecal isotope ratio cholesterol absorption model. Wild type mice (C57BL/6J) and mice deficient in apoprotein E (Apo E KO) were found to absorb from 0.15-0.38% of the [3H]-sitosterol dose into their livers and SCH58235 was found to dose dependently inhibit the absorption and hepatic accumulation of sitosterol (Table 1).

Sitosterolemia is a genetic disorder, which is characterized by increased plasma levels of sitosterol and other plant sterols, due to an increased nonselective intestinal absorption of sterols. Individuals with sitosterolemia have accelerated atherosclerosis, myocardial infarctions, and die at an early age due to extensive coronary atherosclerosis. Drug treatment for sitosterolemia is primarily with bile acid sequestrants (cholestyramine), but compliance is difficult due to constipation. The HMG CoA reductase inhibitors have failed to reduce plasma cholesterol or sitosterol levels in homozygote sitosteroleemics. Current treatments also include ileal bypass surgery and selective low density lipoprotein plasmapheresis. Ezetimibe (SCH58235) may be useful in the treatment of sitosterolemia, by inhibiting the absorption of cholesterol and plant sterols like sitosterol.

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Table 1.

Effect of SCH 58235 on Sitosterol Absorption in Mice

Mouse strain	Treatment	Liver Sitosterol, % of administered Dose average \pm sem	p =
C57BL/6J	Vehicle Control	0.1479 \pm 0.0337	
	SCH 58235-0.3mg/kg	0.1093 \pm 0.0143	
	SCH 58235-1mg/kg	0.0588 \pm 0.0115	0.046
	SCH 58235-3mg/kg	0.0489 \pm 0.0067	0.024
	SCH 58235-10mg/kg	0.0552 \pm 0.0151	0.040
ApoE KO	Vehicle Control	0.3773 \pm 0.0525	
	SCH 58235-0.3mg/kg	0.1863 \pm 0.0246	0.013
	SCH 58235-1mg/kg	0.1019 \pm 0.0225	0.0019
	SCH 58235-3mg/kg	0.0772 \pm 0.0050	0.0023
	SCH 58235-10mg/kg	0.0780 \pm 0.0179	0.0017

Data found in NB 39040, p.64-75
N = 4-6 mice per treatment

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